AMENDMENTS TO CLAIMS

This listing of claims will replace all prior versions, or listings, of claims in this application.

1. (Withdrawn) A composition comprising; a polypeptide forming a hetero-dimer with one processed mammalian caspase-9 monomer (SEQ ID NO:1), said polypeptide having a surface groove from BIR3 (SEQ ID NO:2), or variant thereof, said variant having at least 90% sequence identity with (SEQ ID NO:2) for binding to the mammalian initiator caspase-9, said surface groove including amino acid residues P325, G326, H343, and L344.

2. (Withdrawn) The composition of claim 1 wherein said polypeptide is a variant of a BIR3 surface groove of c-IAP1 (SEQ ID NO:14) or a variant thereof.

3. (Withdrawn) The composition of claim 1 wherein said polypeptide is a variant of BIR3 surface groove of c-IAP2 (SEQ ID NO:15) or a variant thereof.

4. (Withdrawn) The composition of claim 1 wherein said polypeptide is the BIR3 surface groove of XIAP (SEQ ID NO 3).

5. (Withdrawn) The composition of claim 1 wherein the polypeptide includes the BIR-2 (SEQ ID NO: R) repeat or the BIR-1 (SEQ ID NO:20) repeat unit.

6. (Withdrawn) The composition of claim 1 wherein BIR3 (SEQ ID NO: 2) binds to the protein-protein recognition interface of the caspase-9 (SEQ ID NO:1).

7. (Withdrawn) The composition of claim 1 wherein said polypeptide includes one or more zinc ions.

8. (Withdrawn) The composition of claim 1 wherein said polypeptide inhibits activation of procaspase-3 (SEQ ID NO: 10) through inhibition of the mammalian caspase-9 (SEQ ID NO:1).

9. (Withdrawn) The composition of claim 1 wherein the BIR3 (SEQ ID NO:2) domain of said polypeptide bonds to the caspase-9 small subunit (SEQ ID NO:9).

10. (Withdrawn) The composition of claim 1 wherein said polypeptide forms a catalytically inactive complex with the mammalian caspase-9.

11. (Withdrawn) The composition of claim 1 including pharmaceutically-acceptable salts of said polypeptide or variants thereof.

12. (Withdrawn) The composition of claim 1 and a pharmaceutically acceptable excipient.

13. (Withdrawn) A composition comprising; a polypeptide forming a 1:1 complex with a processed mammalian caspase-9 (SEQ ID NO:1), said polypeptide having a surface groove from BIR3 (SEQ ID NO:2) for binding to the mammalian caspase-9, said polypeptide having one or more point mutations of surface groove amino acid residues P325, G326, H343.

14. (Withdrawn) The composition of claim 13 wherein polypeptide is the BIR3 of XIAP (SEQ ID NO:3) or variants and salts thereof.

15. (Withdrawn) The composition of claim 13 wherein said polypeptide is a purified and isolated form of XIAP (SEQ ID NO:13).

16. (Withdrawn) The composition of claim 13 wherein said complex activates procaspase-3 (SEQ ID NO:10).

17. (Withdrawn) The composition of claim 13 wherein said polypeptide is a modified c-IAP1 (SEQ ID NO:14).

18. (Withdrawn) The composition of claim 13 wherein said polypeptide is a modified c-IAP2 (SEQ ID NO:15).

19. (Withdrawn) The composition of claim 13 further comprising an excipient.

20. (Currently Amended) A method of inhibiting ~~the~~ activity of an initiator caspase[[-9]] comprising:

identifying a compound having a structure and function of amino acid residues Pro325, Gly326, His343, and Leu344 of XIAP BIR3, wherein said compound binds to an initiator caspase;

combining the compound with a composition including the initiator caspase; and

inhibiting the activity of the initiator caspase

~~combining processed mammalian caspase-9 (SEQ ID NO:1) with a composition that includes a polypeptide forming a 1:1 complex with said mammalian caspase-9,~~

~~said polypeptide having a surface groove from BIR3 (SEQ ID NO:2) for binding to the mammalian caspase-9 and said surface groove including amino acid residues P325, G326, H343, and L344.~~

21. (Currently Amended) The method of claim 20, wherein the initiator caspase[[-9]] is in one or more cells.

22. (Currently Amended) The method of claim 20, wherein the initiator caspase[[-9]] is present within cells of ~~a mammal subject~~ an individual.

23. (Currently Amended) The method of claim 20, wherein the ~~composition~~ compound further comprises ~~includes~~ an excipient.

24. (Cancelled)

25. (Cancelled)

26. (Withdrawn) A method of making procaspase-9 zymogen comprising: co-expressing the catalytic subunit of caspase-9 in a first vector with a BIR3 domain of XIAP in a second vector in Escherichia coli.

27. (Withdrawn) The method of claim 26 wherein said first vector is pET-21b.

28. (Withdrawn) The method of claim 26 wherein said second vector is pBB75.

29. (Withdrawn) The method of claim 26 wherein said Escherichia coli is strain BL21(DE3)

30. (Withdrawn) The method of claim 26 further comprising purification of said mixture.

31. (Withdrawn) A composition comprising; an isolated polypeptide or variant thereof, said variant having at least 90% sequence identity with BIR3 (SEQ ID NO:2), said polypeptide forming a heterodimer complex with a mammalian caspase -9 (SEQ ID NO:1) and having a surface groove from BIR3 (SEQ ID NO:2) for binding to mammalian initiator caspase, said surface groove including amino acid residues P325, G326, H343, and L344.

32. (Withdrawn) A composition comprising; a polypeptide forming a hetero-dimer with an apoptosome-activated caspase-9 (SEQ ID NO:7), said polypeptide having a surface groove from BIR3 (SEQ ID NO:2), or variant thereof, said variant having at least 90% sequence identity with SEQ ID NO:2 for binding to the apoptosome-activated caspase-9 (SEQ ID NO:7), said surface groove including amino acid residues P325, G326, H343, and L344.

33. (Withdrawn) A composition comprising; a polypeptide forming a hetero-dimer with one mammalian caspase-9 monomer (SEQ ID NO:1), said polypeptide having a

surface groove from BIR3 (SEQ ID NO:2), or variant thereof, said variant having at least 90% sequence identity with (SEQ ID NO:2) for binding to the mammalian initiator caspase-9, said surface groove including amino acid residues P325, G326, and L344.

34. (Withdrawn) The composition of claim 33 wherein said polypeptide is a variant of BIR3 surface groove of c-IAP1 (SEQ ID NO:14).

35. (Withdrawn) The composition of claim 33 wherein said polypeptide is a variant of BIR3 surface groove of c-IAP2 (SEQ ID NO:15).

36. (Withdrawn) The composition of claim 33 wherein said polypeptide is the BIR3 surface groove of XIAP (SEQ ID NO 3) or variant thereof.

37. (Withdrawn) The composition of claim 33 wherein the polypeptide includes the BIR-2 (SEQ ID NO: R) repeat or the BIR-1 (SEQ ID NO:20) repeat unit.

38. (Withdrawn) The composition of claim 33 wherein BIR3 (SEQ ID NO:2) binds to the protein-protein recognition interface of the caspase-9 (SEQ ID NO:1).

39. (Withdrawn) The composition of claim 33 wherein said polypeptide includes one or more zinc ions.

40. (Withdrawn) The composition of claim 33 wherein said polypeptide inhibits activation of procaspase-3 (SEQ ID NO: 21) through inhibition of an initiator caspase.

41. (Withdrawn) The composition of claim 33 wherein the BIR3 (SEQ ID NO: 2) domain of said polypeptide bonds to the caspase-9 small subunit (SEQ ID NO:9) of said caspase-9.

42. (Withdrawn) The composition of claim 33 wherein said polypeptide forms a catalytically inactive complex with the initiator caspase.

43. (Withdrawn) An isolated nucleic acid molecule at least 90% identical to a nucleic acid molecule selected from the group consisting of: a nucleic acid molecule consisting of a nucleotide sequence encoding the amino acid sequence of caspase-9 F404D (SEQ ID NO: 25) wherein said caspase-9 F404D inhibits apoptosis; a nucleic acid molecule consisting of a nucleotide sequence encoding caspase-9 ΔS (amino acid residues 139 to 315 and 331 to 416 of SEQ ID NO:23) wherein said caspase-9 ΔS activates apoptosis; and a nucleic acid molecule consisting of a nucleotide sequence encoding caspase-9 ΔL (amino acid residues 139 to 315 and 339 to 416 of SEQ ID NO:24) wherein said caspase-9 ΔL inhibits apoptosis.

44. (Withdrawn) A vector comprising the nucleic acid molecule of claim 43.

45. (Withdrawn) A host transformed with the vector of claim 44.

46. (Withdrawn) A method for making a caspase-9 polypeptide, comprising: (a) inserting a nucleic acid molecule of claim 1 into a vector; (b) transforming a host with said vector; and (c) culturing said host under conditions to induce expression of the caspase-9 polypeptide (SEQ ID NO:23), (SEQ ID NO:24), or (SEQ ID NO:25) or variants thereof having at least 90% of the sequence identity with said polypeptides.

47. (Withdrawn) A composition comprising: an initiator caspase specific binding agent having a caspase-9 or apoptosome activated caspase-9 recognition binding sequence and caspase-9 inhibiting amino acid residues Pro325, Gly326,His343, and Leu344 in BIR3 of XIAP, wherein the specific binding agent forms a heterodimer complex with an initiator caspase to inhibit its catalytic activity with an procaspase-3.

48. (Withdrawn) The composition of claim 47 wherein the specific binding agent is a peptidomimetic of the BIR3 domain of XIAP.

49. (Withdrawn) The composition of claim 47 wherein the specific binding agent is a polypeptide and variants thereof that are functionally equivalent to the caspase-9 inhibiting amino acid residues Pro325, Gly326,His343, and Leu344 in BIR3 of XIAP.

50. (Withdrawn) A composition comprising: an initiator caspase specific binding agent having a caspase-9 or apoptosome activated caspase-9 recognition binding sequence and including point mutations of the caspase-9 inhibiting amino acid residues functionally equivalent to Pro325, Gly326,His343, and Leu344 in BIR3 of XIAP wherein the specific binding agent forms a heterodimer complex with an initiator caspase to modify its catalytic activity.

51. (Withdrawn) The composition of claim 50 wherein the specific binding agent is a peptidomimetic of the point mutated BIR3 domain of XIAP

52. (Withdrawn) The composition of claim 50 wherein the specific binding agent is a polypeptide.

53. (New) The method of claim 20, wherein the initiator caspase is caspase-9.

54. (New) The method of claim 53, wherein the compound binds to caspase-9 at amino Leu244, Pro237, Phe404, and Phe406.

55. (New) The method of claim 20, wherein the compound forms a 1:1 complex with the initiator caspase.

56. (New) A method for identifying an inhibitor of an initiator caspase comprising:

applying a three-dimensional molecular modeling algorithm to atomic coordinates of caspase-9 to determine coordinates of a binding pocket of caspase-9, said binding pocket comprising at least amino acids Leu244, Pro237, Phe404, and Phe406 of caspase-9;

electronically screening stored spatial coordinates of a set of candidate compounds against spatial coordinates of the binding pocket of caspase-9; and

identifying candidate compounds that bind to the initiator caspase.

57. (New) The method of claim 56, wherein the inhibitory molecule is a peptide or peptidomimetic at least comprising amino acids Pro325, Gly326, His343, and Leu344 of XIAP BIR3.

58. (New) The method of claim 56, wherein the identified inhibitor forms a 1:1 complex with the initiator caspase.

59. (New) The method of claim 56, further comprising:

combining spatial coordinates of portions of the identified inhibitors to provide spatial coordinates of new candidate compounds.

60. (New) An inhibitor of an initiator caspase identified by a method comprising:

applying a three-dimensional molecular modeling algorithm to the atomic coordinates of caspase-9 to determine the coordinates of a binding pocket of caspase-9, said binding pocket comprising at least amino acids Leu244, Pro237, Phe404, and Phe406 of caspase-9;

electronically screening stored spatial coordinates of a set of candidate compounds against spatial coordinates of the binding pocket of caspase-9; and

identifying candidate compounds that binds to the initiator caspase.

61. (New) The inhibitor of claim 60, wherein the identified inhibitor corresponds to at least crystallographic coordinates of amino acid residues P325, G326, H343 and L344 of XIAP BIR3.

62. (New) The inhibitor of claim 60, wherein the identified inhibitor forms a 1:1 complex with the initiator caspase.